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Molecular profiling of Ketamine's rapid antidepressant effect

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One third of the patients with major depressive disorder suffer from treatment resistance and do not respond to commonly used antidepressants. Ketamine, a drug that works through a different mechanism, improves depressive symptoms within hours and is particularly effective in treatment-resistant patients. Scientists at the Max Planck Institute of Psychiatry in Munich have for the first time identified metabolite alterations, affected pathways and biomarker candidates for the Ketamine treatment response in mice. An improved understanding of the molecular events causing the rapid antidepressant effect of Ketamine will allow the development of alternative drugs with a similar mode of action but fewer side effects.

Ketamine, a drug that has been applied as an anesthetic for many years, has recently been shown to have rapid antidepressant activities. The drug is used to treat patients resistant to conventional antidepressants. Unlike other antidepressants, Ketamine improves depressive symptoms already within a few hours, but hallucinogenic side effects in some patients have so far prevented Ketamine's routine use as a first-line drug.

Scientists around Christoph Turck, Research Group Leader at the Max Planck Institute of Psychiatry in Munich, in collaboration with Marianne Müller-Sitz at the University of Mainz, investigated the effects of Ketamine in the hippocampus of mice, a brain region associated with depression. Patients suffering from depression often show impairments in their memory, which is highly dependent on the hippocampus. Further, a dysregulated connectivity network of several brain regions

including the hippocampus was observed in these patients.

In the experiments, molecular changes related to energy metabolism became apparent in the mouse hippocampus cells already two hours after Ketamine treatment. "Mitochondrial abnormalities including alterations in energy metabolism such as glycolysis and citrate cycle have previously been implicated in the pathobiology of affective disorders, such as major depression," explains Katja Weckmann, PhD student and first author of the current study. Two enzymes participating in the citrate cycle are regulated by calcium ions. Ketamine blocks the N-methyl-D-aspartate receptor resulting in a decreased flux of calcium ions into the cells and mitochondria. These changes could lead to an inactivation of the important enzymes and the here observed molecular alterations in energy metabolism.

Whereas the Max Planck researchers found an elevation of glycolytic metabolites in earlier studies investigating treatment with conventional antidepressants, they now observed a reduced activity of glycolysis after Ketamine treatment. Glycolysis results in the release of markedly less energy than the citrate cycle. Taken together, the effects of Ketamine immediately induce molecular alterations and a shift towards the citrate cycle providing a lot of energy for brain cells. Furthermore, through the activation of signalling cascades, Ketamine induces a rapid increase of newly synthesized synaptic proteins and neuronal spines. "All these findings might explain the fast therapeutic onset of Ketamine compared to conventional antidepressants," concludes Christoph Turck.

Understanding these molecular mechanisms might allow the development of alternative drugs with a similar mode of action but fewer side effects. Seven potential metabolite biomarkers in energy metabolism pathways were identified comparing the metabolomics data of Ketamine-treated mice to those of control mice. In the future, physicians might use these biomarkers to assess the response to

Ketamine-related drugs in patients.

More information: "Time-dependent metabolomic profiling of Ketamine drug action reveals hippocampal pathway alterations and biomarker candidates." *Translational Psychiatry* (2014) 4, e481; DOI: 10.1038/tp.2014.119. Published online 11 November 2014. www.nature.com/tp/journal/v4/n … full/tp2014119a.html

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